

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/086414 A1

- (51) International Patent Classification⁷: A61K 31/66, 31/075, C07F 9/02, C07C 43/205
- (21) International Application Number: PCT/US03/11008
- (22) International Filing Date: 10 April 2003 (10.04.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 10 Oct 04
60/371,782 10 April 2002 (10.04.2002) US
- (71) Applicant (for all designated States except US): ARIZONA BOARD OF REGENTS [US/US]; Arizona State University, Box 873511, Tempe, AZ 85287 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): PETTIT, George, R. [US/US]; 6232 Bret Hills Drive, Paradise Valley, AZ 85253 (US). GREALISH, Matthew, P. [US/US]; 863 Sapphire Street, #13, San Diego, CA 92109 (US).
- (74) Agent: ROSENFELD, Susan, Stone; Fennemore Craig, Suite 2600, 3003 North Central, Phoenix, AZ 85012-2913 (US).
- (81) Designated States (national): CA, JP, US.
- (84) Designated States (regional): European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).
- Declarations under Rule 4.17:**
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations CA, JP, European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)
 - of inventorship (Rule 4.17(iv)) for US only
- Published:**
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STRUCTURAL MODIFICATION OF RESVERATROL: SODIUM RESVERASTATIN PHOSPHATE

(57) Abstract: Described herein are novel compounds having antineoplastic and antimicrobial activity, obtained via structural modifications of resveratrol and combretastatin A-4, methods for synthesis of these compounds, and their use in pharmaceutical composition and for use in the treatment of mammals having cancer. Examples of the novel compounds are: (Z)- and (E)- 3,4',5'-trimethoxystilbene (4a, 4b); (Z)- and (E)-3,5-dimethoxy-4'-hydroxystilbene (14c, 14d); (Z)- and (E)-3-hydroxy-4',5-dimethoxystilbene (14g, 14h); (Z)- and (E)-3,5-dihydroxy-4'-methoxy-stilbene (14k, 14l); sodium resverastatin dibenzyl phosphate ((Z)-3,5-dimethoxy-4-[O-bis(benzyl)phosphoryl]-stilbene) (14m); and sodium resverastatin phosphate (14n).

WO 03/086414 A1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/11008

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/66, 31/075; C07F 9/02; C07C 43/205
US CL : 514/109, 720, 721; 568/17, 646

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/109, 720, 721; 568/17, 646

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	SPATH et al. Constituents of red sandalwood. III. Synthesis of pterostilbene. Ber. February 1941, Vol. 74B, pages 189-192, especially page 189.	2, 7 and 12 ----- 2, 7 and 12
Y	GRACZA et al. High-performance liquid chromatographic separation and quantitative determination of plant stilbene derivatives. Journal of Chromatography. April 1984, Vol. 287, No. 2, pages 462-265, especially page 463	3 and 13
X --- Y	RYU et al. Antitumor Activity of some Phenolic Components in Plants. Arch. Pharm. Res. January 1994, Vol. 17, No. 1, pages 42-44, especially page 43.	3, 13 and 17 ----- 3, 13 and 17
A	WO 01/60774 A1 (BRIGHAM YOUNG UNIVERSITY) 23 August 2001 (23.08.01), page 1, lines 24-30; and page 3, line 11 to page 7, line 19.	6-10
X, E --- Y, E	US 2003/0118617 A1 (SOBY et al) 26 June 2003 (26.06.03), paragraphs 0007, 0015, 0019, 0021 and claim 1.	1-3, 11-13, 15-17 ----- 1-3, 11-13, 15-17

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

21 August 2003 (21.08.2003)

Date of mailing of the international search report

16 SEP 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Rosalind Keys

Telephone No. 703-308-1235

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2002/0028852 A1 (GHAI et al) 07 March 2002 (07.03.02), paragraphs 0003, 0012, 0013, 0016, 0017, 0019 and Table I.	1, 11 and 15 ----- 1, 11 and 15
X --- Y	CUSHMAN et al. Synthesis and evaluation of analogs of (Z)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene as potential cytotoxic and antimitotic agents. Journal of Medicinal Chemistry. June 1992, Vol. 35, No. 12, pages 2293-2306, especially pages 2294-2298.	1, 5, 6, 11 and 15 ----- 1, 5, 6, 11 and 15
X --- Y	TAKAOKA, MICHIO. The Synthesis of Resveratrol and its Derivatives. Proceedings of the Imperial Acadamey(Tokyo). October 1940, Vol. 16, pages 405-407, especially compounds (I) and (VIII).	1 and 2 ----- 1, 2, 11 and 12
Y, P	RIMANDO et al. Cancer Chemopreventive and Antioxidant Activities of Pterostilbene, a Naturally Occuring Analogue of Resveratrol. Journal of Agricultural and Food Chemistry. June 2002, Vol. 50, No. 12, pages 3453-3457, especially page 3454, column 1.	2, 12 and 16
X, P	PETTIT et al. Antineoplastic Agents. 465. Structural Modification of Resveratrol: Sodium Resverastatin Phosphate. Journal of Medicinal Chemistry. May 2002, Vol. 45, No. 12, pages 2534-2542.	1-18

INTERNATIONAL SEARCH REPORT

PCT/US03/11008

Continuation of B. FIELDS SEARCHED Item 3:
EAST, CAS ONLINE
search terms: resveratrol, cancer, tumor, hydroxy, methoxy